# Complete Summary

## GUIDELINE TITLE

Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.

## BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 28 p. (Technology appraisal guidance; no. 117).

## GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

- End-stage renal disease
- Secondary hyperparathyroidism

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

### CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Nephrology

### INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

### GUIDELINE OBJECTIVE(S)

To establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of secondary hyperparathyroidism for people on dialysis due to end-stage renal disease

### TARGET POPULATION

Patients with secondary hyperparathyroidism in end-stage renal disease and on maintenance dialysis therapy

### INTERVENTIONS AND PRACTICES CONSIDERED

1. Cinacalcet
2. Regular monitoring of the response to treatment

### MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Mortality
    - Incidence of cardiovascular events
    - Incidence of fractures
    - Health-related quality of life
    - Symptoms related to hyperparathyroidism
    - Plasma parathyroid hormone, calcium, phosphate, and calcium x phosphate product levels
    - Parathyroidectomy
    - Hospitalization
    - Adverse effects
- Cost-effectiveness

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases
Searches of Unpublished Data

## DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

**Note from the National Guideline Clearinghouse (NGC)**: The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group, Peninsula Medical School (see the "Availability of Companion Documents" field.)

### Clinical Effectiveness

### Inclusion and Exclusion Criteria

*Inclusion*

Intervention:

Cinacalcet hydrochloride (HCI) in licensed doses

Comparators:

Placebo or "Standard care", which may include:

- Phosphate binders
- Vitamin D
- Parathyroidectomy

Population:

People with hyperparathyroidism secondary to end-stage renal disease (ESRD) on peritoneal or haemodialysis

Study Design:

Randomised controlled trials (RCTs) with at least 12 weeks follow up

Outcomes:

- Mortality
- Incidence of cardiovascular events
- Incidence of fractures
- Health related quality of life
- Symptoms related to hyperparathyroidism
- Serum PTH, calcium, phosphate and calcium x phosphate product levels
- Parathyroidectomy
- Hospitalisation

- Adverse effects

*Exclusion Criteria*

Population:

- People with renal disease not on dialysis
- Primary hyperparathyroidism

Study Design:

- RCTs with less than 12 weeks follow up
- Study designs other than RCTs

**Search Strategy**

Electronic databases were searched for published systematic reviews, RCTs, economic evaluations and ongoing research in March 2005 and updated in February 2006. Appendix 8.4 of the Assessment Report (see "Availability of Companion Documents" field) shows the databases searched and the strategy in full. Bibliographies of articles were also searched for further relevant studies, and the U.S. Food and Drug Administration (FDA) website was searched for relevant material.

**Identification of Studies**

Relevant studies were identified in two stages. Abstracts returned by the search strategy were examined independently by two researchers and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers examined these independently for inclusion or exclusion and disagreements were resolved by discussion. The process is illustrated in Appendix 8.5 of the Assessment Report (see "Availability of Companion Documents" field).

**Cost-Effectiveness**

**Search Strategy**

Electronic databases were searched using the strategy shown in Appendix 3 of the Assessment Report (see "Availability of Companion Documents" field).

**Inclusion and Exclusion Criteria**

Studies were included if they were cost-utility analyses of cinacalcet compared with standard treatment for people with end-stage renal disease on dialysis with secondary hyperparathyroidism.

**NUMBER OF SOURCE DOCUMENTS**

**Clinical Effectiveness**

The systematic review identified seven published reports of randomized controlled trials (RCTs) of cinacalcet versus placebo in people with hyperparathyroidism secondary to end-stage renal disease who were receiving dialysis. Most of these publications reported on one or more of four RCTs sponsored by the manufacturer of cinacalcet, although three smaller RCTs were also identified. In addition, the manufacturer submitted information on an unpublished study relating to an RCT designed to evaluate optimal levels of concomitant vitamin D and phosphate binders in patients receiving standard care with or without cinacalcet.

### Cost-Effectiveness

- No cost-utility studies in the relevant populations were identified.
- One cost-utility study was submitted to the National Institute for Health and Clinical Excellence (NICE) appraisal process by the manufacturer.

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

## METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

**Note from the National Guideline Clearinghouse (NGC)**: The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group, Peninsula Medical School (see the "Availability of Companion Documents" field.)

### Data Extraction Strategy

Data were independently extracted by two researchers. Disagreements were resolved by discussion. Actual numbers were extracted where possible. In some cases data had to be extracted from graphs and may be subject to inaccuracies. Such data is identified in the data extraction sheets. Data extraction forms for each included study are shown in Appendix 7 of the Assessment Report (see the "Availability of Companion Documents" field).

### Quality Assessment Strategy

Assessments of randomised controlled trial (RCT) quality were performed using the indicators shown below. Results were tabulated and these aspects described.

*Internal Validity*

Sample Size

Power calculation at design

Selection Bias

- Explicit eligibility criteria
- Proper randomisation and allocation concealment
- Similarity of groups at baseline

Performance Bias

Similarity of treatment other than the intervention across groups

Attrition Bias and Intention to Treat Analysis

- All patients are accounted for
- Number of withdrawals specified and reasons described
- Analysis undertaken on an intention to treat (ITT) basis

Detection Bias

- Blinding
- Objective outcome measures
- Appropriate data analysis

Any potential conflict of interest was noted (for example, financial support provided to studies and/or authors by manufacturers of the interventions).

*External Validity*

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group in practice. Study findings can only be effectively generalisable if they (a) describe a cohort that is representative of the affected population at large or (b) present sufficient detail in their outcome data to allow the reader to extrapolate findings to a patient group with different characteristics.

Generalisability of included studies was assessed by examining the age, sex, and race profile of the included patients, as well as their baseline mineral and parathyroid hormone (PTH) serum levels. Studies that were representative of the United Kingdom (UK) population with regard to these factors were judged to have high external validity.

**Methods of Analysis**

Details of the methodology and results of included trials are tabulated and described in the text of the Assessment Report (see the "Availability of Companion

Documents" field). Results from RCTs are presented in the same tables; where study design renders cells inapplicable, they have been greyed out. Dashes in the tables indicate the information was not reported. Where calculated by the authors, chi-square statistics were derived using the CHIDIST function of Microsoft Excel.

The assessment group did not combine the results using meta-analysis because the major trials have already been reported in combination using patient level data.

Most of the papers report outcome measure in metric units. The assessment group has adjusted these in order to present them in standard units using the conversion factors shown in Table 13 of the Assessment Report (see the "Availability of Companion Documents" field.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

### Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

### Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document'

(ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

**Who is on the Appraisal Committee?**

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

The systematic review carried out by the Assessment Group did not identify any published cost-effectiveness studies relevant to the scope of this appraisal. An economic model and separate cost–consequence analysis were submitted by the manufacturer of cinacalcet, and the Assessment Group developed its own economic model. Both models were cost–utility analyses comparing cinacalcet in addition to standard care (using vitamin D and phosphate binders) with standard care only in patients with secondary hyperparathyroidism (parathyroid hormone [PTH] >31.6 pmol/litre) who were receiving dialysis. Both analyses adopted the perspective of the National Health Service (NHS), and generally similar cost and resource-use assumptions were used. There were, however, differences between the models in the assumptions driving effectiveness.

The model submitted by the manufacturer incorporated health states reflecting patients' status in relation to adverse events associated with secondary hyperparathyroidism. Clinical events included in the analysis were cardiovascular hospitalisations, fractures (major and minor), parathyroidectomies, and death. The effect of cinacalcet on the relative risks for these outcomes was based on the pooled results of four clinical trials. The manufacturer's model resulted in an incremental cost-effectiveness ratio (ICER) of 35,600 pounds sterling per quality-adjusted life year (QALY) gained. Subgroup analyses in patients with moderate (PTH 31.6 to 84.2 pmol/litre) and severe (PTH > 84.2 pmol/litre) secondary hyperparathyroidism resulted in ICERs of 30,400 pounds sterling and 48,300 pounds sterling per QALY gained respectively. Various one-way sensitivity

analyses were conducted. The results of these indicated that the ICER was most sensitive to variations in the dose of cinacalcet.

The Assessment Group's approach differed from that of the manufacturer in that they modelled the effect of treatment on PTH levels and then related this intermediate endpoint to clinical events. In the base-case analysis, patients in both arms were stratified by PTH levels. These were defined as 'controlled' (PTH 32 pmol/litre or less), 'uncontrolled' (PTH 33 to 84 pmol/litre) or 'very uncontrolled' (PTH 85 pmol/litre or more). Patients in the 'very uncontrolled' group were stratified further according to whether or not they had undergone parathyroidectomy (with or without adverse surgical events). Clinical events included cardiovascular events, fractures and death, and the probabilities of these occurring at different PTH levels were derived from a variety of different sources, mostly large cohort studies. These estimates of probability rely on a number of assumptions and are subject to uncertainty. The reduction in utility associated with an adverse event was greater in the 3 months after the event than in subsequent cycles of the model. Utility increased for subsequent cycles, but to a level that was lower than the utility before the event. The costs associated with cinacalcet, the treatment of adverse events, parathyroidectomy, monitoring of patients and concomitant medications were included in the model. It was assumed that a proportion of patients with 'very uncontrolled' PTH levels, and no patients with 'controlled' or 'uncontrolled' PTH levels, would be taking non-calcium-based phosphate binders. A wide range of sensitivity analyses were conducted. The costs of dialysis were excluded from the base-case analysis but included in a sensitivity analysis.

See section 4.2 in the original guideline document for a detailed discussion of cost effectiveness models from the manufacturer and the Assessment Group.

### METHOD OF GUIDELINE VALIDATION

External Peer Review

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

- Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.
- Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:
    - Who have "very uncontrolled" plasma levels of intact parathyroid hormone (defined as greater than 85 pmol/litre [800 pg/mL]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, **and**
    - In whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits
- Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma levels of intact parathyroid hormone of 30% or more is seen within 4 months of treatment, including dose escalation as appropriate.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate use of cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy

### POTENTIAL HARMS

The most commonly reported adverse effects in clinical trials were nausea and vomiting. These were mild to moderate in nature and transient in most cases.

For full details of side effects and contraindications, see the Summary of Product Characteristics (SPC), available at http://emc.medicines.org.uk/.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

Because cinacalcet lowers calcium levels, it is contraindicated if serum calcium is below the lower limit of the normal range.

For full details of contraindications, see the Summary of Product Characteristics (SPC), available at http://emc.medicines.org.uk/.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

#### Implementation

- The Healthcare Commission assesses the performance of National Health Services (NHS) organizations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on NICE website (www.nice.org.uk/TA114) (see also the "Availability of Companion Documents" field).
    - Local costing template incorporating a costing report to estimate the savings and costs associated with implementation.
    - Audit criteria to monitor local practice

### IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources

Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 28 p. (Technology appraisal guidance; no. 117).

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2007 Jan

### GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

### SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

### GUIDELINE COMMITTEE

Appraisal Committee

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 2 p. (Technology appraisal 117). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Costing statement: Hyperparathyroidism - cinacalcet HCI. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 2 p. (Technology appraisal 117). Available from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. Audit criteria. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 11 p. (Technology appraisal 117). Available from the National Institute for Health and Clinical Excellence (NICE) Web site.
- The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease patients on dialysis: a systematic review and economic evaluation. Assessment report. Peninsula Technology Assessment Group (PenTAG), University of Southampton. 2006 Mar 16. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1184. 11 Strand, London, WC2N 5HR.

## PATIENT RESOURCES

The following is available:

- Cinacalcet for treating secondary hyperparathyroidism in people with kidney disease who are on dialysis. Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jan. 5 p. (Technology appraisal 117).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1185. 11 Strand, London, WC2N 5HR.

authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

### NGC STATUS

This NGC summary was completed by ECRI Institute on June 26, 2007.

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Date Modified: 9/29/2008